which were not well described in this article, although the probability may be low. In addition, regarding the feasibility of dynamic HCC risk prediction,[4] it would be interesting to determine whether the SAGE-B model is predictive from baseline, and compare the predictive accuracy among CAGE-B, SAGE-B, and other existing risk models such as mREACH-B, at 5 years.[9]

In conclusion, this study provides insight for risk re-assessment of HCC development by establishing new risk prediction models for HCC development in patients with CHB receiving prolonged AVT beyond 5 years. Further validation studies on Asian patients with CHB are required before widespread use of CAGE-B and SAGE-B models can be implemented.

Financial support

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2019R1 A2C4070136). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: S.U. Kim; Analysis, interpretation of the data: H.A. Lee, and B.K Kim; Drafting of the manuscript: H.A. Lee; Critical revision of the manuscript for important intellectual content: S.U. Kim; Obtained funding: S.U. Kim; Administrative, technical, or material support: S.U. Kim; Study supervision: S.U. Kim.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.02.023.

References

Author names in bold designate shared co-first authorship

[1] Papatheodoridis GV, Sypsa V, Dalekos GN, Yurdaydin C, Van Boemmel F, Buti M, et al. Hepatocellular carcinoma prediction beyond year 5 of oral therapy in a large cohort of Caucasian patients with chronic hepatitis B. J Hepatol 2020;72(6):1088–1096.
[2] **Kim MN**, **Kim SU**, Park JY, Kim DY, Han KH, Chon CY, et al. Risk assessment of liver-related events using transient elastography in patients with chronic hepatitis B receiving entecavir. J Clin Gastroenterol 2014;48:272–278.
[3] **Kim BS**, **Seo YS**, **Kim YS**, Lee CH, Lee HA, Kim SU, et al. Reduced risk of hepatocellular carcinoma by achieving a subcirrhotic liver stiffness through antiviral agents in hepatitis B virus-related advanced fibrosis or cirrhosis. J Gastroenterol Hepatol 2018;33:503–510.
[4] **Jeon MY**, **Lee HW**, Kim SU, Kim BK, Park JY, Kim DY, et al. Feasibility of dynamic risk prediction for hepatocellular carcinoma development in patients with chronic hepatitis B. Liver Int 2018;38:676–686.
[5] Kim BG, Park NH, Lee SB, Jeon S, Park JH, Jung SW, et al. The risk of hepatocellular carcinoma within and beyond the first 5 years of entecavir in Korean patients with chronic hepatitis B. Liver Int 2018;38:2269–2276.
[6] **Kim SU**, **Seo YS**, Lee HA, Kim MN, Lee EJ, Shin HJ, et al. Hepatocellular carcinoma risk steadily persists over time despite long-term antiviral therapy for hepatitis B: a multicenter study. Cancer Epidemiol Biomarkers Prev 2020;29(4):832–837.
[7] Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444–1453.
[8] Zhang X, Wong GL-H, Wong VW-S. Application of transient elastography in nonalcoholic fatty liver disease. Clin Mol Hepatol 2020;26(2):128–141.
[9] **Lee HW**, **Yoo EJ**, Kim BK, Kim SU, Park JY, Ahn SH, et al. Prediction of development of liver-related events by transient elastography in hepatitis B patients with complete virological response on antiviral therapy. Am J Gastroenterol 2014;109:1241–1249.

Han Ah Lee[1]
Beom Kyung Kim[2,3]
Seung Up Kim[2,3,*]
[1]*Department of Internal Medicine, Institute of Gastroenterology, Korea University College of Medicine, Seoul, Korea*
[2]*Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea*
[3]*Yonsei Liver Center, Severance Hospital, Seoul, Korea*
[*]Corresponding author. Address: Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea. Tel.: 82-2-2228-1930, fax: 82-2-393-6884.
E-mail address: KSUKOREA@yuhs.ac (S.U. Kim)

Reply to: "Clinical relevance of dynamic risk assessment for developing hepatocellular carcinoma during prolonged antiviral therapy"

To the Editor:

We thank Lee and colleagues for their interest and comments about our recent article on the prediction of hepatocellular carcinoma (HCC) risk in patients with chronic hepatitis B (CHB) under long-term (>5 years) nucleos(t)ide analogue (NA) therapy, which remains of great interest for many investigators.

Regarding their comments, Lee *et al.* first cited 3 studies which further support our main concept that dynamic assessment of liver stiffness (LS) can be useful for HCC prediction.[1–3] However, the results of those studies cannot replace our stronger findings (1,427 patients) for accurate HCC prediction beyond year-5,[4] as the first 2 had small patient numbers (162 and 209) and quite short follow-up and prediction (2 years).[1,2] In addition, the third study (1,397 patients) reported data on just 5-year HCC prediction based on dynamic changes of HCC

Received 4 March 2020; accepted 8 March 2020; available online 28 March 2020
https://doi.org/10.1016/j.jhep.2020.03.014

risk scores,[3] which was initially reported by others for earlier scores.[5]

We agree that some studies from East Asia did not confirm the decline of HCC risk after 5 years of NA therapy[6,7] which was restricted only to our Caucasian patients with cirrhosis.[4] This is not surprising given the epidemiological, clinical and virological differences between patients in Europe and East Asia. It should be also noted that the suboptimal diagnosis of baseline cirrhosis (absence of liver biopsies) in the Asian studies might also have played some role in those seemingly conflicting results, whereas possible type II errors, at least for the study of BG Kim *et al.*, cannot be excluded.[6]

We never claimed that CAGE-B could accurately express the change between fibrotic burden determined at baseline by any method (liver biopsy in most of our cases) and at year-5 by LS. Moreover, although it cannot be excluded, we never supported that LS changes or even CAGE-B/SAGE-B or any other score can definitely predict the individual HCC risk, particularly for marginal cases like the one mentioned by Lee *et al.* Instead, we suggested that the most important and clinically relevant characteristic of CAGE-B, which scores age in relation to baseline cirrhosis combined by dichotomous assessment of year-5 LS (≥/<12 kPa), is its 100% negative predictive value for HCC using the low-risk cut-off offering the option of no surveillance in this subgroup.[4]

As Lee *et al.* commented, our study did not aim to assess HCC prediction in all patients with CHB treated with entecavir/tenofovir, as HCC prediction in the first 5 years can be based on our PAGE-B score.[8] Since, however, the previous scores did not accurately predict HCC beyond year 5,[4,9] CAGE-B and SAGE-B scores were developed to specifically predict HCC risk after year-5 representing 2 simple and reliable risk scores for such late HCC prediction. As mentioned in our paper, these new scores must be prospectively validated further in other Caucasian cohorts and other clinical settings including Asian cohorts before their widespread use can be implemented.

Conflict of interest

GV Papatheodoridis: advisor/lecturer for Dicerna, Gilead, Ipsen, Merck Sharp & Dohme, Spring Bank; research grants from Gilead. P Lampertico: speaking bureau/advisor for Abbvie, Eiger, Gilead, GlaxoSmithKline, Janssen, Merck/ Merck Sharp & Dohme, MYR Pharma, Roche.

Authors' contributions

GV Papatheodoridis: Conception and design of the letter; Analysis and interpretation of data; Drafting of the manuscript; Approval of the final version of the manuscript. P Lampertico: Design of the letter; Interpretation of data; Drafting of the manuscript; Approval of the final version of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.03.014.

References

[1] Kim MN, Kim SU, Park JY, Kim DY, Han KH, Chon CY, et al. Risk assessment of liver-related events using transient elastography in patients with chronic hepatitis B receiving entecavir. J Clin Gastroenterol 2014;48:272–278.

[2] Kim BS, Seo YS, Kim YS, Lee CH, Lee HA, Kim SU, et al. Reduced risk of hepatocellular carcinoma by achieving a subcirrhotic liver stiffness through antiviral agents in hepatitis B virus-related advanced fibrosis or cirrhosis. J Gastroenterol Hepatol 2018;33:503–510.

[3] Jeon MY, Lee HW, Kim SU, Kim BK, Park JY, Kim DY, et al. Feasibility of dynamic risk prediction for hepatocellular carcinoma development in patients with chronic hepatitis B. Liver Int 2018;38:676–686.

[4] Papatheodoridis GV, Idilman R, Dalekos GN, Buti M, Chi H, van Boemmel F, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444–1453.

[5] Wong GL, Chan HL, Chan HY, Tse PC, Tse YK, Mak CW, et al. Accuracy of risk scores for patients with chronic hepatitis B receiving entecavir treatment. Gastroenterology 2013;144:933–944.

[6] Kim BG, Park NH, Lee SB, Jeon S, Park JH, Jung SW, et al. The risk of hepatocellular carcinoma within and beyond the first 5 years of entecavir in Korean patients with chronic hepatitis B. Liver Int 2018;38:2269–2276.

[7] Kim SU, Seo YS, Lee HA, Kim MN, Lee EJ, Shin HJ, et al. Hepatocellular carcinoma risk steadily persists over time despite long-term antiviral therapy for hepatitis B: a multicenter study. Cancer Epidemiol Biomarkers Prev 2020;29(4):832–837.

[8] Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800–806.

[9] Voulgaris T, Papatheodoridi M, Lampertico P, Papatheodoridis GV. Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B. Liver Int 2020;40:484–495.

George V. Papatheodoridis[1,*]
Pietro Lampertico[2,3]

[1]*Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece*

[2]*Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico - Division of Gastroenterology and Hepatology - CRC "A. M. and A. Migliavacca" Center for Liver Disease, Milan, Italy*

[3]*Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy*

[*]Corresponding author. Address: Department of Gastroenterology, School of Medicine, National and Kapodistrian University of Athens, Laiko General Hospital of Athens, 17 Agiou Thoma street, 11527 Athens, Greece. Tel: +30 2132061115, Fax: +30 2107462601.
E-mail address: gepapath@med.uoa.gr (G.V. Papatheodoridis)